Remarks

The invention features *ex vivo* expanded anti-angiogenic T cells ("EAT cells"). EAT cells can attack tumor vasculature while sparing normal vasculature (see pages 29-30 of the specification). The selective ability of EAT cells to attack tumor vasculature compared to normal vasculature can be assessed by determining the toxicity of the cells towards HUVEC in the presence and absence of Hsp47. Cells that are toxic towards HUVEC in the absence, but not the presence of Hsp47 include EAT cells (see page 20 of the specification). CIK cells and certain other T cells can be EAT cells (see pages 2-3 of the specification).

Claims 2, 5, 9-13, 23, 26-33 and 59 have been cancelled. Claims 60-63 have been added. Support for these new claims is found, for example, on pages 20 and 31 of the specification.

Rejections Under 35 U.S.C. §102(b)

The Examiner rejected claims 1 and 9-21 as allegedly anticipated by Lu et al. (J. Immunol. 153:1687, 1994).

First, the fact the *ex vivo* expanded cells selectively damage tumor vasculature compared to normal vasculature is a characteristic of the cells, not an intended use, and as such must be accorded patentable weight.

Second, in rejecting claims 1 and 9-21 the Examiner provided basis for asserting that the *ex vivo* expanded cells described by Lu et al. inherently selectively damage tumor vasculature compared to normal vasculature or that the cells "inherently contain receptors that recognize Hsp47". Moreover, inherent anticipation "may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *Mehl/Biophile International Corp. v. Milgraum*, 192 F.3d 1362 (Fed. Cir. 1999) (emphasis is original). Thus, it is Applicant's position, that the Examiner has not demonstrated that original claims 1-33 and 59 are anticipated.

However, to expedite prosecution, Applicants have incorporated the limitations of claims 2 and 5, neither of which were rejected under 35 U.S.C. §102(b), into amended claim 1. Claims 3, 4, 6-8 and 14-22 depend directly or indirectly from claim1. Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. §102(b) be withdrawn.

New claims 60-63 are drawn to a "composition comprising *ex vivo* expanded CIK cells wherein at least 2% (claim 60) of the *ex vivo* expanded CIK cells kill cultured HUVEC cells in the absence, but not in the presence of Hsp47 and a pharmaceutically acceptable carrier". As explained on page 20 of the specification, the selective ability of CIK cells to attack tumor vasculature compared to normal vasculature can be assessed by determining the toxicity of the CIK cells towards HUVEC in the presence and absence of Hsp47. This is demonstrated in Example 9 of the specification (page 31), which shows that HUVEC are protected from CIK-mediated lysis by an Hsp47-GST fusion protein, but not by GST. Nothing in Lu et al. teaches or suggests the composition of claims 60-63. Thus, these claims are not anticipated by Lu et al.

Rejections Under 35 U.S.C. §112, second paragraph

"composition"

The Examiner rejected claims 1-33 and 59 as indefinite for the use of the term "composition". The Examiner states that the term is indefinite because "composition implies two or more components." The Examiner went on to state that as "currently interpreted, the composition only contains one item, namely, ex vivo cells" First, Applicants have claimed a "composition comprising" certain cells. Applicants are entitled to use comprising language in a composition claim without specifying the other components in the composition. The composition can contain other unspecified components and this does not render the claims indefinite. Second, Applicants have amended claim 1 to specify that the composition comprises a pharmaceutically acceptable carrier.

"selectively"

The Examiner rejected claim 1 as indefinite for including the term "selectively" because, according to the Examiner, "it is unclear as to the degree of selection required." Applicant has amended claim 1 to include the limitation of claim 2 specifying 2-fold selectivity. Claims 3, 4, 6-8 and 14-22 depend directly or indirectly from claim1.

"antigen"

The Examiner rejected claims 12 and 13 as indefinite for including the term "antigen". Applicant has cancelled claims 12 and 13, thereby obviating this rejection.

"or a part thereof"

The Examiner rejected claim 18 for reciting "or a part thereof" with respect to IL-12. Applicant has amended claim 18 to remove the phrase "or a part thereof", thereby obviating this rejection.

"immuno-modulator"

The Examiner rejected claim 32 for reciting " immuno-modulator". Applicant has cancelled claim 32, thereby obviating this rejection.

Rejections Under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 1-33 and 59 as allegedly not enabled. The Examiner stated that the specification was enabling for a composition comprising CIK cells. However, the Examiner argued that the specification is not enabling for: "T cells or NK cells (in general)"; cells that "comprise a regulable suicide gene"; compositions "comprising chemotherapeutic agents", "agents (which include antibodies, bi-specific antibodies)", compounds (which includes covalently or non-covalently associated compounds such as toxins, antibodies, detectable labels, immuno-modulators, and radioactive compounds), or immuno-modulators."

Applicants have amended claim 1 to recite that composition comprises "ex vivo expanded CIK cells." Claims 23, 26-33 and 59 have been cancelled, obviating the Examiner's rejections related to suicide genes, agents, compounds, and immunomodulators other than bi-and multi-specific antibodies in respectfully submitted adjusted claims 24 and 25 (please see below.) Claim 22 is drawn to a composition that also comprises a chemotherapeutic agent. Those skilled in the art know many chemotherapeutic agents and how such agents should be administered. The literature on the appropriate use of chemotherapeutic agents is vast. In view of the art and the skill of those in the art regarding chemotherapeutic agents, the use of chemotherapeutic agents in the claimed compositions is clearly enabled.

With regard to claims 24 and 25, immunologists skilled in the art know how to perform the selection of suitable antibodies/scaffolds and of how to prepare such reagents. In addition, those skilled in the art know many suitable mono-, bi- and multi-specific antibodies and molecular scaffolds and how to selected and administer such agents. In view of the art and the skill of those in the art regarding bi-and multi-specific antibodies and molecular scaffolds, the use of such agents in the claimed compositions is clearly enabled.

In view of the forgoing, Applicant respectfully requests that the rejections under 35 U.S.C. §112, first paragraph, be withdrawn.